(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 3 078 412 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
12.10.2016 Bulletin 2016/41

(51) Int Cl.:
B01D 65/10 *(2006.01)* ***G01M 3/20*** *(2006.01)*

(21) Application number: **16162802.9**

(22) Date of filing: **30.03.2016**

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME
Designated Validation States:
MA MD

(30) Priority: **08.04.2015 US 201562144553 P**

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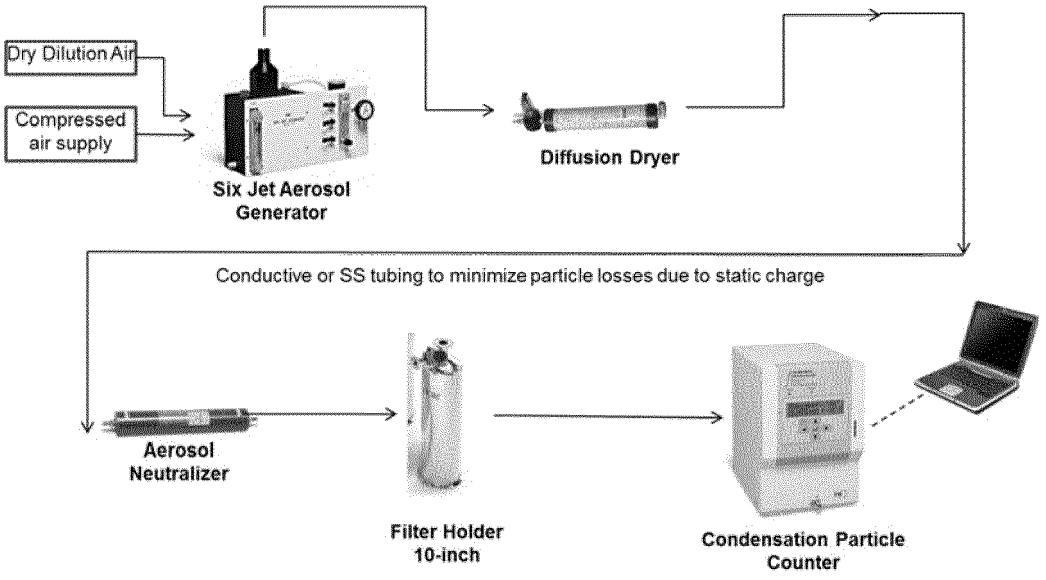
(54) ENHANCED AEROSOL TEST FOR ASSESSING FILTER INTEGRITY

(57) A method of aerosol integrity testing of filters, capable of detecting single defects that are less than 20 μm in diameter, and even as small as 2 μm in diameter, in liquid sterilizing grade filters such as filter cartridges. The method challenges the filter in a dry state with a particle stream of aerosol particles of the appropriate size and in the appropriate concentration, such that at least one or more of the particles in the stream will penetrate a defective region or regions within the membrane but will not penetrate in the integral region of the membrane. Wetting of the filter is not required.

FIG. 8



EP 3 078 412 A1

Description

[0001] This application claims priority of U.S. Provisional Application Serial No. 62/144,553 filed April 8, 2015, the disclosure of which is incorporated herein by reference.

FIELD OF THE DISCLOSURE

[0002] The present disclosure generally relates to a method for integrity testing filters, such as liquid sterilizing grade filters.

BACKGROUND

[0003] High purity filtration of media, such as in the fields of biotechnology, chemistry, electronics, pharmaceuticals, and the food and beverage industries requires the use of sophisticated filter modules that are not only capable of a high degree of separation, but that will tend to prevent contamination of the environment, of the medium to be filtered, and of the resulting filtrate. This is designed to prevent unwanted, often dangerous organisms, such as bacteria or viruses, as well as environmental contaminants, such as dust, dirt, and the like from entering into the process stream and end product. To ensure sterility of the filtrate, filter modules must maintain their integrity throughout the filtration process. Accordingly, integrity testing of sterilizing filters is a fundamental requirement of critical process filtration applications in the pharmaceutical industry, and is used to identify filters containing oversized pores or defects that can compromise the retention performance of the filter. FDA guidelines recommend integrity testing of filter modules prior to use and after filtration. Typically this testing is initially performed after steam sterilization to ensure that the filter is not damaged; accordingly, care must be taken to ensure that sterility of the filter, and thus the filtrate, is not compromised. Post-processing, the filter integrity test is performed again *in situ* to detect whether the filter was compromised during use. This information can be used to alert operators to a potential problem immediately after processing, and to quickly take corrective action. Further, FDA guidelines require that integrity testing documentation be included with batch product records.

[0004] There are a variety of methods of integrity testing, including the diffusion test and the pressure hold test. The diffusion test measures the rate of gas transfer through a filter to be tested. At differential gas pressures below the bubble point, gas molecules migrate through water-filled pores of a wetted membrane following Fick's Law of Diffusion. The gas diffusional flow rate for a filter is proportional to the differential pressure and the total surface area of the filter. At a pressure approximately 80% of the minimum bubble point, the gas which diffuses through the filter membrane can be measured to determine a filter's integrity. A diffusional flow reading exceeding a value stated by the manufacturer indicates a variety of problems, including an incorrect temperature, wrong pore size, incompletely wetted membrane, non-integral membrane or seal, or inadequate stabilization time. The pressure hold test, also known as the pressure decay or pressure drop test, is a variation of the diffusion test. In this test, a highly accurate gauge is used to monitor upstream pressure changes due to gas diffusion through the filter. Because there is no need to measure gas flow downstream of the filter, any risk to downstream sterility is eliminated.

[0005] These tests require that the filter be wetted, which is a time and water-consuming process. The sensitivity of these tests is also limited in part due to background noise inherent in these tests.

[0006] Compared to traditional integrity tests such as gas/liquid diffusion, aerosol integrity testing has a number of advantages including fast test times, and no required wetting of the filter. Aerosol integrity testing has been used in the pharmaceutical industry for detecting defects in HEPA and ULPA grade filters. This test is also used for filters providing sterile gas. However, there are no known applications of aerosol testing to assess the integrity of filters for sterilizing liquids. Aerosol integrity testing has been considered to be unsuitable for liquid filters because particle capture in gases can occur by a number of mechanisms that are not functional in liquids. Mechanisms such as electrostatic attraction and diffusional deposition can result in interception of particles in a filter element, so that penetration of particles through defects is not assured. While aerosol integrity testing has been demonstrated to reliably detect relatively large defects (> 100 μm), it has not been previously known how to detect defects on the order of 20 μm or less; i.e., defects that could compromise the retention performance of a liquid sterilizing grade filter. Liquid sterilizing grade filters are defined in the FDA "Aseptic Guideline" (FDA "Guideline on Sterile Drug Products Produced by Aseptic Processing", Division of Manufacturing and Product Quality, Rockville, MD, June 1987) as those capable of totally retaining a B. diminuta challenge level of 10^7 cfu/cm^2 at a differential pressure of 30 psi.

[0007] It therefore would be desirable to provide a methodology for aerosol testing of filters that does not suffer from the drawbacks of the prior art.

SUMMARY

[0008] The problems of the prior art are addressed by the embodiments disclosed herein, which relate to an aerosol integrity test of filters. In certain embodiments, the method is capable of detecting single defects that are less than 20 μm in diameter, and even as small as 2 μm in diameter, in liquid sterilizing grade filters, such as liquid sterilizing grade filter cartridges, for example. The test can be carried out without destroying the filter. Since the filter need not be wetted, it also need not be dried upon completion of the test. In certain embodiments, the method includes generating aerosol particles of the appropriate size and in the appropriate concentration, challenging the filter with the particle stream at a condition such that at least one or more of the particles in the stream will penetrate a defective region or regions within the membrane but will not penetrate in the integral region of the membrane, and detecting any particles that penetrate a defective region. Because an integral filter will not exhibit any particle passage, the detection of only a single or a few particles indicates a defect.

[0009] In accordance with certain embodiments, the method allows for the non-destructive integrity testing of a sterilizing grade filter in a dry state. In certain embodiments, the method achieves a higher defect detection sensitivity than conventional aerosol tests and conventional gas/liquid diffusion and bubble point tests. In certain embodiments, the method allows for faster integrity testing than conventional methods. In certain embodiments, the filter is a pleated filter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] For a better understanding of the present disclosure, reference is made to the accompanying drawings, which are incorporated herein by reference and in which:

FIG. 1 is a graph of particle count rate vs. nominal defect size for various membranes;
FIG. 2 is a plot of particle count rate vs. nominal defect size;
FIG. 3 is a graph of particle count rate vs. defect size for a PES membrane;
FIG. 4 is a graph of particle count rate vs. defect size for a PVDF membrane;
FIG. 5 is a graph of NaCl particle counts vs. number of atomizer jets;
FIG. 6 is a plot of air flow rate vs. nominal defect size;
FIG. 7 is another plot of air flow rate vs. nominal defect size; and
FIG. 8 is a schematic diagram showing a test setup in accordance with certain embodiments.

DETAILED DESCRIPTION

[0011] The sensitivity of an integrity test is constrained by its ability to differentiate the signal for a defect from any background noise that can compete or interfere with the signal. For example, for the conventional air diffusion integrity test that is commonly used to assess the integrity of sterilizing grade liquid filters, even perfectly integral filters will exhibit a significant diffusion flow rate through the liquid layer in the filter. This diffusive flow rate is sensitive to filter thickness, filter porosity, pore tortuosity, and operating condition variables such as temperature and test pressure. A defect in the filter will allow for a convective flow rate in excess of the diffusion flow rate but this excess flow rate must be high enough to be clearly distinguishable from the typical range of diffusion flow rates in integral devices. For small defects, the convective flow rate through a defect can be masked by the diffusional flow through the integral portion of the filter.

[0012] Ideally, the background noise in an integrity test is as close to zero as possible. In the case of aerosol testing, the number of particles that are able to penetrate an integral filter should be zero, so that the detection of any particle that has penetrated a filter is an unambiguous signal for a defect.

[0013] It has been found that sterilizing grade filters (often designated as 0.22 μm rated filters) retain 100% of aerosol particles in the size range between about 10 nm and 800 nm. In certain embodiments, suitable particles include NaCl particles, KC1 particles, as well as other materials that are commonly used to generate aerosols. Other common materials include di(2-ethylhexyl) phthalate(DOP), polystyrene (PSL) and polystyrene-divinylbenzene (PS-DVB) latex spheres, and powders and dusts such as silica, uranium-dioxide, coal, carbon black, pollens, and Arizona road dust (ARD).

Table 1 below shows particle penetration as a function of particle size for PVDF membranes with nominal pore size ratings between 0.1 and 5 μm:

TABLE 1

PVDF Membrane	Pore Rating (μm)	Cumulative Particle Penetration (%)
Sample 1	0.1	0
Sample 2	0.2	0

(continued)

PVDF Membrane	Pore Rating (μm)	Cumulative Particle Penetration (%)
Sample 3	0.45	0
Sample 4	0.65	0
Sample 5	1	0.0000089
Sample 5	5	1.2
Aerosol solution: 0.1 g/l NaCl Aerosol Inlet concentration: 6.5x x 10^6 p/cc		

[0014] It can be seen that for membranes with nominal pore size rating less than about 1 μm, the retention efficiency is 100%. If a defect exists however, then particles smaller than the defect size will have the potential to penetrate the filter.

[0015] In accordance with certain embodiments, the method of integrity testing a filter includes providing a liquid sterilizing grade filter to be tested, wherein the filter is not pre-wetted (dry); generating an aerosol particle stream wherein the particles in the stream have a suitable size and a suitable concentration to challenge the filter and penetrate a defective region in the filter without penetrating integral regions in the filter; applying the aerosol stream to the filter for a predetermined period of time, and detecting particles that penetrate the defective region. For sterilizing grade filters, suitable particle concentrations may be in the range 10^5 to 10^7 particles/cm^3, and particle sizes may be in the range 10-1000 nm in diameter. In certain embodiments, the method is able to detect single defects that are less than 20 μm in diameter, and as small as 2 μm in diameter. In certain embodiments, one or more of the solids concentration of the particle stream (typically 10^5 - 10^7 particles/cm^3), the pressure at which the aerosol is created (typically 5-60 psig), and the number of atomizer generators (from 1 to 6, for example) is modified to ensure passage of particles through defects. In certain embodiments, the amount of time the aerosol particle stream is applied to the filter is modified to allow for sufficient resolution of small rates of particle passage. For example, if the rate of particles that penetrate the membrane is less than one particle per minute, then several minutes can be allowed to ensure that the particle passage rate is accurately determined. With respect to particle concentration, pressure, number of atomizers, and length of time the aerosol stream is applied, these parameters are determined for each type of filter, and can then be applied for all filters of that type.

[0016] In certain embodiments, the filters are pleated filters, such as PVDF pleated filters. Pleated filters are typically made with the filter media folded in an accordion-like fashion. The filters may be spiral pleated filters. The filter element may be a membrane. In certain embodiments, the filters, such as pleated filters, are housed in a cartridge.

EXAMPLE 1

[0017] In order to assess the capability of the aerosol test to identify defective filters, cylindrical holes of sizes between 2 μm and 20 μm were laser drilled into 142-mm membrane discs. Two types of membranes were evaluated: a 0.2 μm rated sterilizing grade PVDF membrane and a 0.2 μm rated sterilizing grade PES membrane. These membrane filters were challenged with a NaCl aerosol stream (0.12 g/l NaCl, 3 x 10^6 p/cc aerosol inlet concentration) generated using a TSI model 3076 aerosol generator at test conditions recommended by the aerosol equipment supplier. The aerosol generator pressure was set at 30 psig and the particles were counted for one minute. The aerosol particles were counted using a TSI model 3772 condensation particle counter. A suitable test set up is shown in FIG. 8. FIG. 1 shows that while the integral membrane showed no passage of particles, the membranes with the laser hole defects showed very high passage of particles. This test demonstrates that particles could readily pass through the defects and be detected by the particle counter. The integral membranes did not exhibit any particle passage.

EXAMPLE 2

[0018] Sterilizing grade membranes in pleated cartridge format were tested under the same conditions, including aerosol and test pressure, as the 142 mm discs described in Example 1. As was done with the 142 mm discs, pleated 10" cartridges were constructed with membranes containing single laser hole defects between 2 μm and 20 μm. It can be seen from FIG. 2 that in pleated cartridge format, the defect signal was much reduced compared to flat discs. Defect sizes that were easily detected in 142 mm discs (containing about 127 cm^2 of membrane area) format were not detectable in 10" pleated cartridge (containing about 5000 cm^2 of membrane area) format. No particle penetration was detected in the PES membrane cartridge containing a 2 μm hole, or, in a PVDF membrane cartridge containing a 5 μm hole. This was in part due to the more tortuous pathway that the particles must travel in a pleated membrane, which also contains

porous upstream and downstream support layers. The tortuous pathway hinders access to the membrane surface, and therefore increases the opportunity for particle interception either upstream or downstream of the defect and upstream of the particle detector. In addition, as membrane area increases, the flow through the defect becomes an increasingly smaller portion of the flow through the entire membrane and therefore there is a dilution effect on the measured downstream sample.

[0019] To overcome the low passage of particles through small defects in 10" pleated membrane filters, the concentration and flow rate of particles challenging the filter were increased. Particle concentration can be increased by increasing the solids concentration in the atomizer solution, increasing the pressure at which the aerosol is created, and increasing the number of atomizer generators. In addition, the test was run for at least 5 minutes to allow for sufficient resolution of small rates of particle passage. This is in contrast to the typical practice of aerosol testing in which the test is often terminated in one minute or less. An enhanced combination of aerosol test conditions were developed and are summarized in Table 2:

TABLE 2

Condition	Number of Atomizers	NaCl Concentration (w/w %)	Atomizer Pressure (psig)
Standard	1	0.012	30
Enhanced	5	1.2	50

TABLE 3

Membrane Type	Particle Type	Defect Size (μm)	Particle Penetration Rate (p/l/min)
PES	NaCl	None	<1
		5	148
	KC1	None	<1
		5	180
PVDF	NaCl	None	<1
		5	215
	KC1	None	<1
		5	273

EXAMPLE 3

[0020] The PES and PVDF membrane cartridges were also tested using a standard air diffusion integrity test. The cartridges were wetted and then the air diffusion flow rate was measured using a test pressure of 40 psig. FIGS. 6 and 7 show that while the air diffusion flow rate was slightly elevated for cartridges containing defects smaller than about 10-15 μm compared to the integral controls, the increase in flow rate was not enough to differentiate integral from non-integral devices. Typical flow rate ranges of integral cartridges is indicated by the shaded areas in the plots. Defects less than 20 microns could not be detected.

Claims

1. A method of integrity testing a filter in the dry state, comprising:

providing a liquid sterilizing grade filter to be tested in a dry state;
generating an aerosol particle stream wherein the particles in said stream have a suitable size and a suitable concentration to challenge said filter and penetrate any defective region in said filter but will not penetrate integral regions in said filter; and
detecting particles that penetrate said defective region.

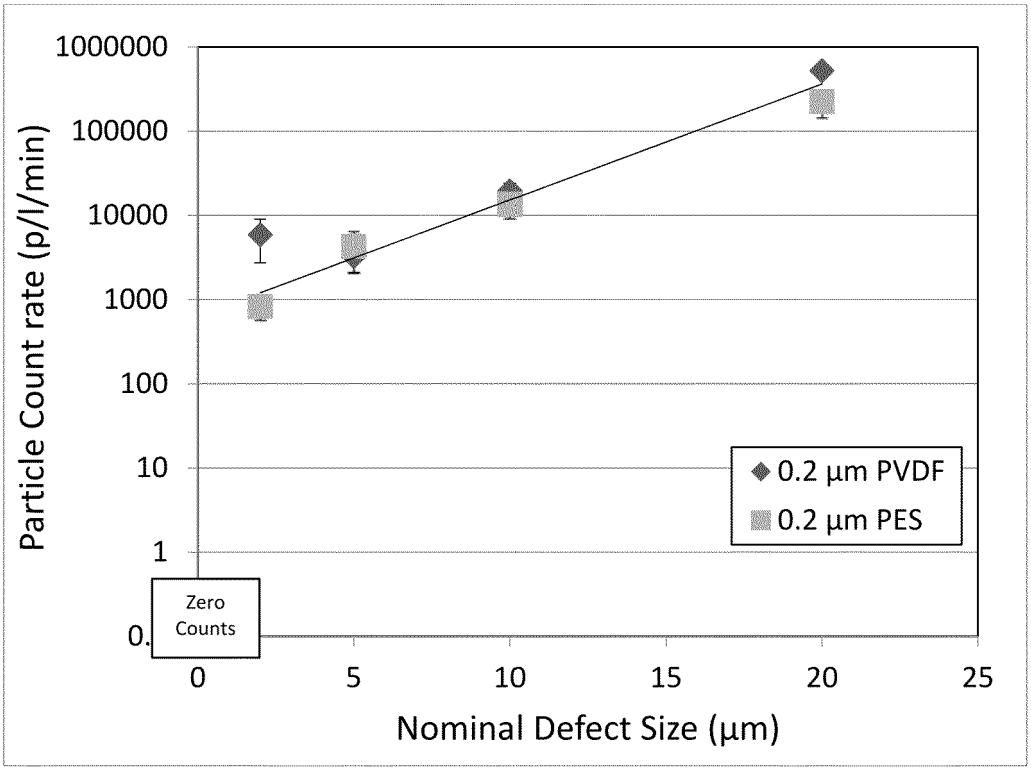
2. The method of claim 1, wherein particles that penetrate defects in said filter that are as small as 2 microns are detected.

3. The method of claim 1, wherein said filter is pleated.

4. The method of claim 1, wherein said filter is housed in a cartridge.

5. The method of claim 1, wherein said aerosol particle stream comprises NaCl.

FIG. 1



Aerosol solution: 0.12 g/l NaCl
Aerosol inlet concentration: $3x10^6$ p/cc
Each point average of 3 discs
Error bars represent standard deviation

FIG. 2

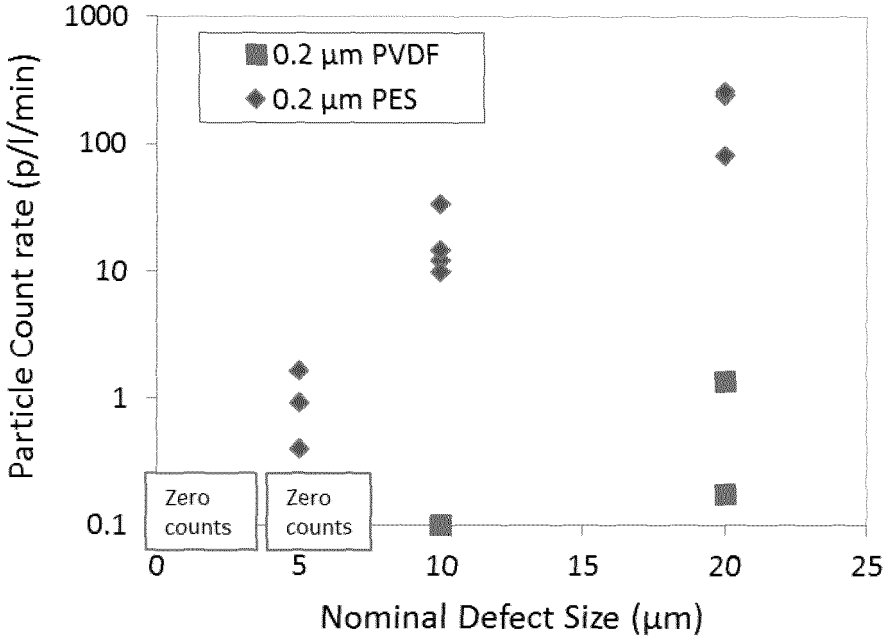

1000
100
10
1
0.1
Particle Count rate (p/l/min)
0.2 µm PVDF
0.2 µm PES
Zero counts
Zero counts
0
5
10
15
20
25
Nominal Defect Size (µm)

FIG. 3

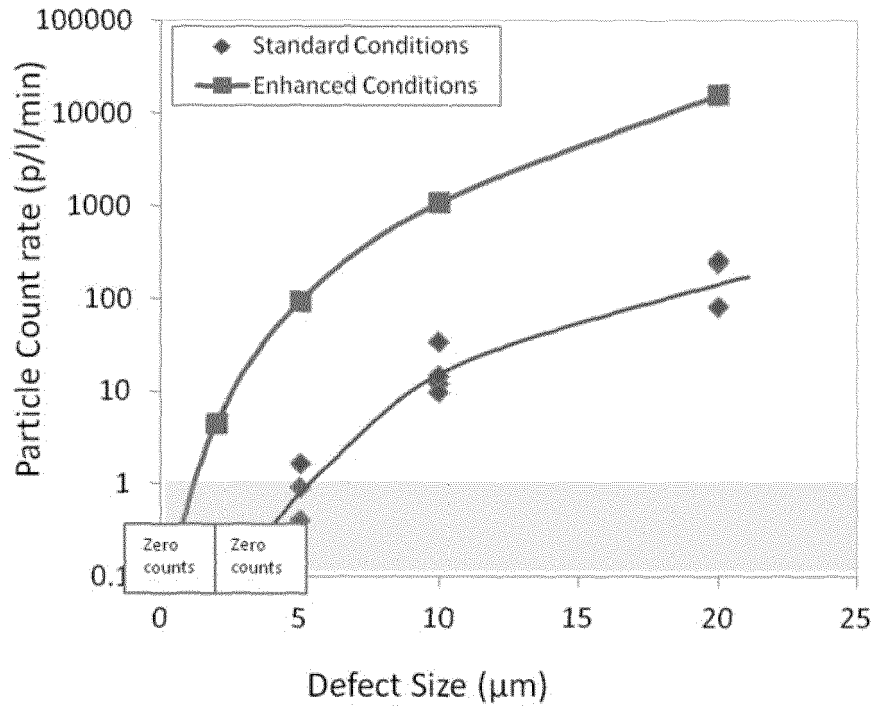

100000
10000
1000
100
10
1
0.1
Particle Count rate (p/l/min)
Standard Conditions
Enhanced Conditions
Zero counts
Zero counts
0
5
10
15
20
25
Defect Size (µm)

FIG. 4

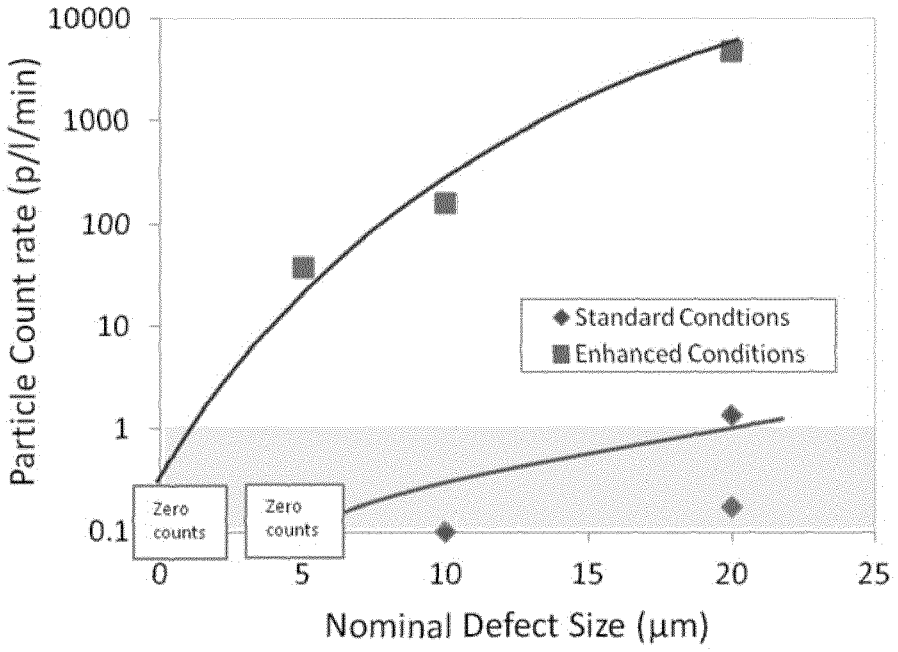

10000
1000
100
10
1
0.1
Particle Count rate (p/l/min)
Standard Condtions
Enhanced Conditions
Zero counts
Zero counts
0
5
10
15
20
25
Nominal Defect Size (µm)

FIG. 5

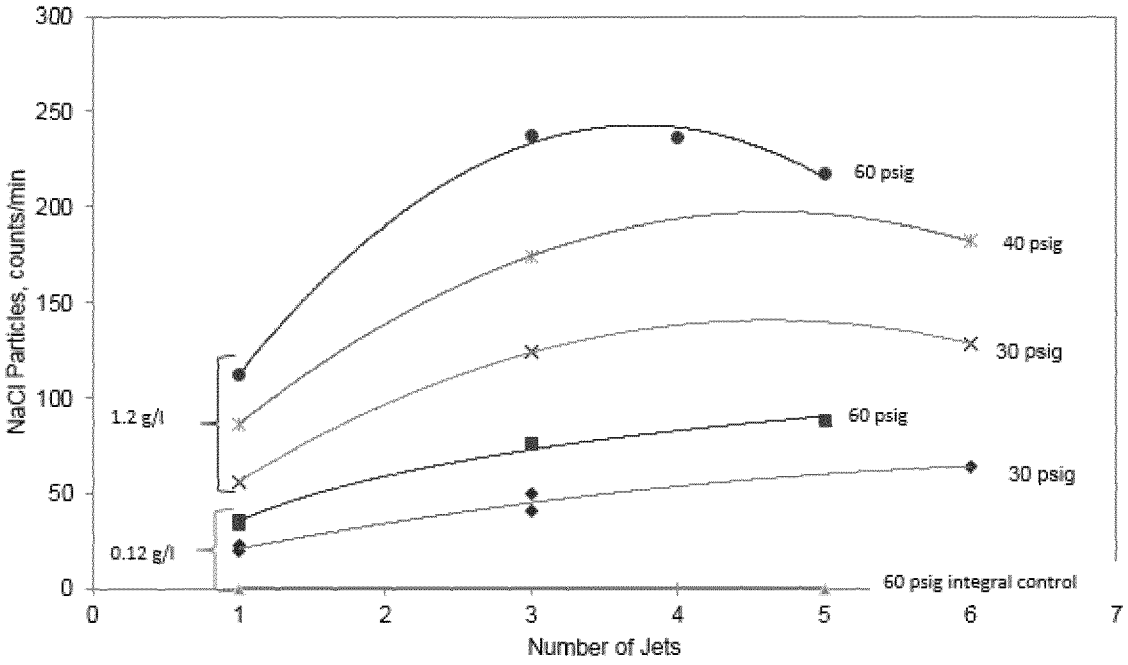

300
250
200
150
100
50
0
NaCl Particles, counts/min
60 psig
40 psig
30 psig
60 psig
30 psig
60 psig integral control
1.2 g/l
0.12 g/l
0
1
2
3
4
5
6
7
Number of Jets

FIG. 6

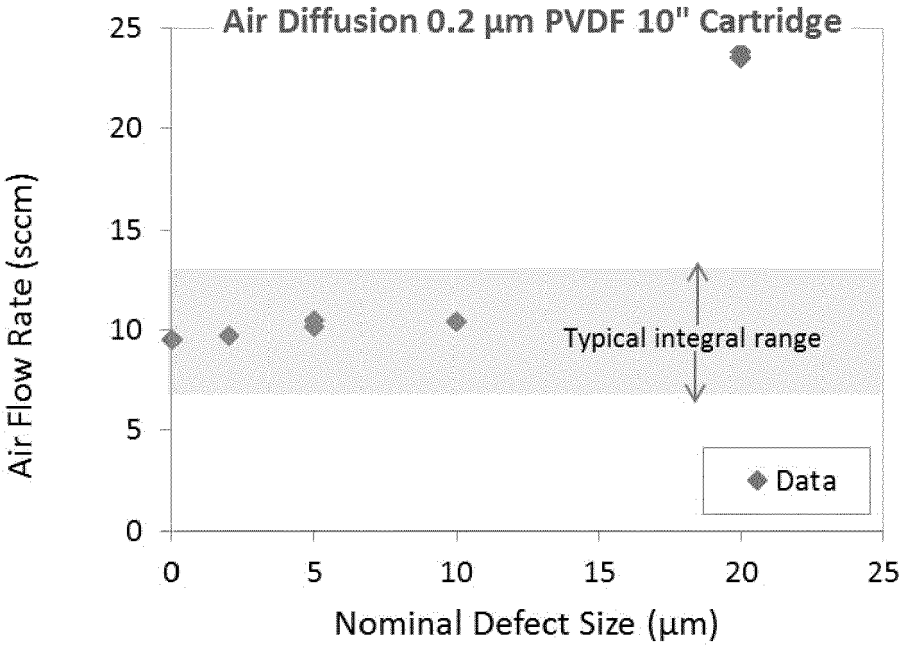

Air Diffusion 0.2 µm PVDF 10" Cartridge
Air Flow Rate (sccm)
Nominal Defect Size (µm)
Typical integral range
Data
0
5
10
15
20
25

FIG. 7

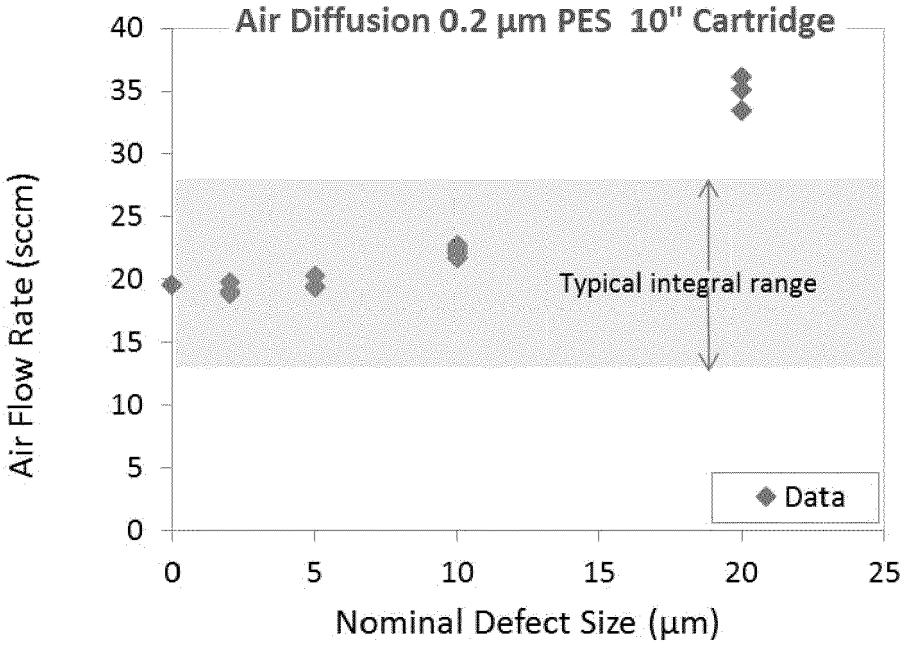
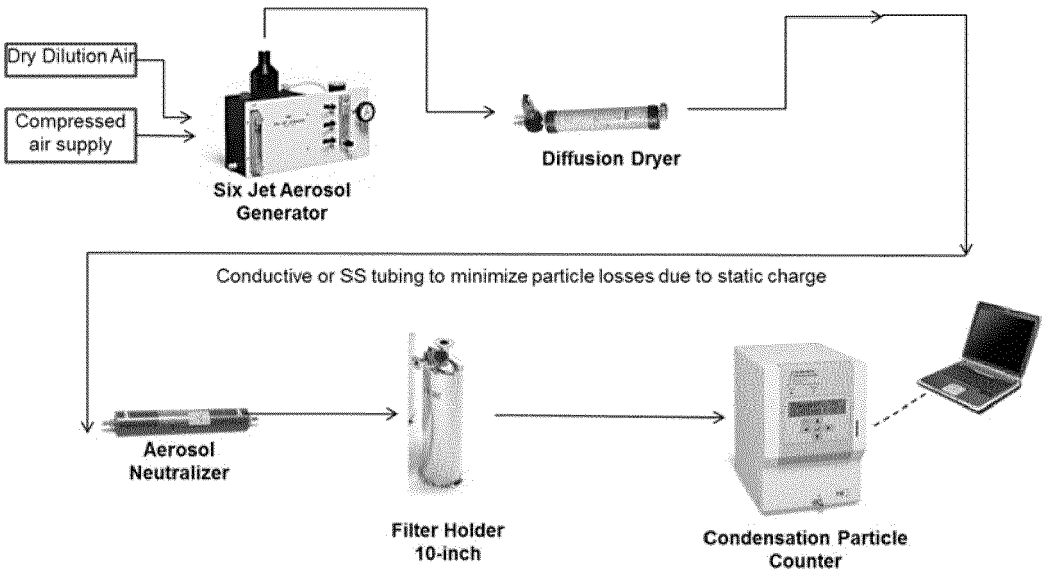

Air Diffusion 0.2 µm PES 10" Cartridge
Air Flow Rate (sccm)
Nominal Defect Size (µm)
Typical integral range
Data
0
5
10
15
20
25
30
35
40

FIG. 8


Dry Dilution Air
Compressed air supply
Six Jet Aerosol Generator
Diffusion Dryer
Conductive or SS tubing to minimize particle losses due to static charge
Aerosol Neutralizer
Filter Holder 10-inch
Condensation Particle Counter

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EUROPEAN SEARCH REPORT

Application Number
EP 16 16 2802

DOCUMENTS CONSIDERED TO BE RELEVANT

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	2 August 2016	Marti, Pedro

CATEGORY OF CITED DOCUMENTS

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REFERENCES CITED IN THE DESCRIPTION

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